ACUTE TOXICITY SUMMARY

CARBON TETRACHLORIDE

(carbon chloride; carbon tet; freon 10; halon-104; methane tetrachloride; necatrine; tetrachlorocarbon; tetrachloromethane; tetraform; tetrasol; univerm)

CAS Registry Number: 56-23-5

I. Acute Toxicity Summary (for a 7-hour exposure)

Inhalation reference exposure level	**1,900 μg/m³**
Critical effect(s)	toxicity to the developing fetus
Hazard Index target(s)	Reproductive/developmental; Nervous System; Alimentary Tract

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid
Molecular formula	CCl_4
Molecular weight	153.24
Density	1.59 g/cm^3 @ 20°C
Boiling point	76.54°C
Melting point	-23°C
Vapor pressure	91.3 mm Hg @ 20°C
Flashpoint	critical temperature = 283.1°C
Explosive limits	not found
Solubility	soluble in acetone, ethanol, benzene, carbon disulfide; moderately soluble in water
Odor threshold	96 ppm (604 mg/m³) (Amoore and Hautala, 1983)
Odor description	sweet, chloroform-like odor
Metabolites	chloroform; carbene radical, carbon monoxide (Ahr *et al.*, 1980)
Conversion factor	1 ppm = 6.3 mg/m³

III. Major Uses or Sources

Carbon tetrachloride is used as a solvent for the recovery of tin in tin-plating waste and in the manufacture of semiconductors. It is also used in petrol additives, refrigerants, metal degreasing, and as a catalyst in the production of polymers. Carbon tetrachloride is also used as a chemical intermediate in the production of fluorocarbons and pesticides (HSDB, 1994).

IV. Acute Toxicity to Humans

Hepatotoxicity is the most sensitive and best studied toxic endpoint for CCl_4 exposure (Andrews and Snyder, 1991). The human data on hepatic effects of CCl_4 are based on numerous clinical case reports with poorly defined exposure conditions. The hepatotoxic effects, which may occur more readily in persons regularly consuming alcohol, are often reversible over the course of several weeks (Fry *et al*., 1959).

Bioactivation of CCl_4 into reactive metabolites by hepatic cytochrome P-450 enzymes results in hepatic centrilobular degeneration and necrosis (Andrews and Snyder, 1991). After a single dose of CCl_4, evidence of centrilobular necrosis is visible within 12 hours and obvious necrosis occurs by 24 hours. If no further injury occurs, the lesions begin to repair after 24 hours, and may be restored to normal after 14 days recovery. A reduction of P450 activity in the liver also occurs and is due to irreversible binding by reactive metabolites and subsequent inhibition of the P450 enzymes that metabolize CCl_4 (Andrews and Snyder, 1991).

Mucosal irritation and CNS effects have also been reported following CCl_4 exposure. In one of the first controlled human studies on the effects of CCl_4, Davis (1934) observed headaches, nausea, and vomiting in subjects exposed to 317 ppm (1,997 mg/m^3) for 30 minutes. Stewart *et al*. (1961) exposed 6 human volunteers to 49 ppm (309 mg/m^3) CCl_4 for 70 minutes, or to 10-11 ppm (63-69 mg/m^3) CCl_4 for 3 hours. The subjects reported no irritation to the eyes or respiratory tract. A Romberg test and a heel to toe test (tests of central nervous system function) were normal in these subjects immediately following exposure, but one individual had elevated urine urobilinogen levels 7 days following exposure. The magnitude of the elevation of urinary urobilinogen was not given. Two of 4 individuals exposed to 49 ppm (309 mg/m^3) CCl_4 also exhibited decreased serum iron, although in one the decrease was still within the normal range.

Predisposing Conditions for CCl_4 Toxicity

Medical: Individuals with compromised liver function may be more susceptible to CCl_4-induced hepatotoxicity.

Chemical: Co-exposure to ethanol, acetone, or isopropanol is known to potentiate the toxicity of carbon tetrachloride (Charbonneau *et al*., 1986; Cornish and Adefuin, 1966). Exposure to other chlorinated compounds, such as chlordecone, also potentiates the toxicity of CCl_4 (Curtis *et al*., 1979).

V. Acute Toxicity to Laboratory Animals

A concentration of 7,300 ppm (45,990 mg/m^3) CCl_4 was reported to be lethal to 1 out of 10 rats after a single, 2-hour exposure (Adams *et al*., 1952). In this study, one rat out of 30 died after a 10-hour exposure to 3,000 ppm (18,900 mg/m^3). Delayed effects from these exposures included weight loss, abnormal behavior and appearance, and additional mortality. Rats surviving these exposures exhibited liver injury evidenced by serum phosphatase, increased prothrombin clotting time, fatty degeneration, and enlargement of the liver.

A 4-hour inhalation exposure to 250 ppm (1,575 mg/m^3) CCl_4 resulted in increased serum glutamic-oxalacetic transaminase (SGOT) activity in rats, indicative of hepatic damage (Cornish and Block, 1960). Exposure of these rats to a concentration of 100 ppm for 4 hours did not result in changes in SGOT activity.

Kim and coworkers (1990) showed that administration of a range of concentrations from 10 mg/kg to 1,000 mg/kg CCl_4 by gavage to rats resulted in a dose-dependent increase in serum levels of hepatic enzymes, decrease in hepatic cytochrome P-450 activity, and an increase in centrilobular lesions in the liver. In this study, 10 mg/kg was the LOAEL for hepatocellular changes and elevated serum enzymes. At low doses, the hepatocellular effects of CCl_4 are reversible, while at higher doses necrosis and irreversible damage occur (Gerhard *et al*., 1970).

In addition to its hepatocellular toxicity, CCl_4 also has been shown to affect the immune system. Mice exposed orally to 500 mg/kg CCl_4 exhibited suppressed T-cell dependent immune responses as measured by decreased splenic antibody forming cells. These mice also had elevated plasma interleukin-2 and transforming growth factor-β1 measured 24 and 48 hours after exposure (Delaney *et al*., 1994). However, a previous study showed that hepatotoxicity from CCl_4 occurs at much lower concentrations than does toxicity to the immune system (Smialowitz *et al*., 1991).

A physiologically-based pharmacokinetic model for carbon tetrachloride has been developed in the rat (Paustenbach *et al*., 1988). In this model, it was estimated that 60% of inhaled CCl_4 is metabolized, and that 96% of the metabolized CCl_4 forms biological adducts which degrade slowly with a half-life of 24 hours. The remaining 4% of the metabolized CCl_4 becomes CO_2.

VI. Reproductive or Developmental Toxicity

No studies were available on the reproductive effects of CCl_4 in humans. Significant decreases in fetal body weight, crown-rump length, and ossification of sternebrae were observed in rats exposed to 300 ppm (1,890 mg/m^3) CCl_4 on days 6-15 gestation (Schwetz *et al*., 1974). High doses (0.3 ml/100 g body weight) of CCl_4 injected intraventricularly caused marked histologic injury to the chorionic epithelium of the placenta in rats (Tsirel'nikov and Tsirel'nikova, 1976). Carbon tetrachloride has not been listed as a developmental toxicant under Proposition 65.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Mild Adverse Effect Level

Because the most sensitive endpoint found in the inhalation toxicity literature was developmental toxicity, a potentially disabling effect, there is no mild adverse effect level available for CCl_4.

Reference Exposure Level (protective against severe adverse effects for a 7 hour exposure): 0.3 ppm (1,900 μg/m³)

Because of the uncertainty in extrapolating from repeated dose studies to a one-hour concentration, for the reproductive/developmental endpoint, we have chosen to use a single day exposure as the basis for the REL. Thus, the REL for CCl_4 is for a 7 hour exposure.

Study	Schwetz *et al*. (1974)
Study population	pregnant rats
Exposure method	inhalation exposure to 0, 300, or 1,000 ppm for 7 hours/day on days 6-15 of gestation
Critical effects	fetal growth retardation (decreased crown-rump length and body weight)
LOAEL	300 ppm
NOAEL	not determined in this study
Exposure duration	7 hours/day
LOAEL uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1,000
Reference Exposure Level	0.3 ppm (1.9 mg/m³; 1,900 μg/m³)

Level Protective Against Life-threatening Effects

Rats (5-30 per group, males and females) were exposed to single concentrations of CCl_4 for durations varying from 6 minutes to 10 hours (Adams *et al*., 1952). Concentrations used ranged from 3,000 to 19,000 ppm (45,990 to 119,700 mg/m³) CCl_4. Mortality was measured for several weeks following the exposure.

1-Hour Mortality Data in Rats from CCl_4 Inhalation

Concentration (ppm x 10^3)	7.3	8.4	9.4	10.8	12.0	12.0	15.4	17.8	19.0	24.0
Response	0/20	0/20	1/10	1/10	3/10	4/10	7/10	8/10	9/19	20/20

Adams et al. (1952)

A benchmark dose approach used a log-normal probit analysis (Crump, 1983) of rat lethality data from Adams *et al*. (1952). Exposure durations from 1-4 hours were included in the analysis. Concentrations of CCl_4 were adjusted to approximate equivalent 1-hour concentrations using the equation $C^n * T = K$, where n = 2.8 (ten Berge *et al*., 1986). The concentration associated with a 5% incidence of lethality was 8,557 ppm (53,909 mg/m³); the benchmark concentration (BC_{05}) for this response, the 95% lower confidence limit on this concentration, was 7,010 ppm

(44,163 mg/m³). An uncertainty factor (UF) of 3 was applied to the BC_{05} to account for interspecies variation since the BC_{05} accounts for some degree of individual variation and a UF of 10 was used to account for human individual variability. The total UF was 30.

level protective against life-threatening effects= BC_{05} /(UF)

The level protective against life-threatening effects for CCl_4 is therefore 234 ppm (1,470 mg/m³). The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for 1% and 5% response rates are compared below. Refer to section IX of this toxicity summary for the graphic representation of benchmark concentration derivation.

Response rate	MLE (ppm)	95% LCL (ppm)
1%	6,646	4,976
5%	8,557	7,010

NIOSH (1995) lists a revised IDLH of 200 ppm based on acute inhalation toxicity in humans.

VIII. References

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